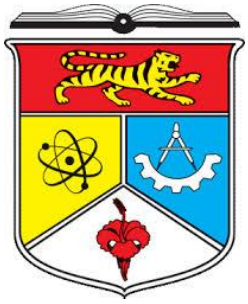

THESIS PROPOSAL

Doctor of Internal Medicine (Dr. Int. Med.)

# A RANDOMISED OPEN – LABEL CONTROLLED TRIAL OF PLEURAL IRRIGATION WITH NORMAL SALINE VERSUS INTRAPLEURAL FIBRINOLYTIC WITH TISSUE PLASMINOGEN ACTIVATOR AND DNase IN PLEURAL INFECTION

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# Chapter 1 : INTRODUCTION

Pneumonia thought to be the chief aetiological process in the development of pleural space infection is defined as an infection of the lung parenchyma with an estimated annual incidence rate of 5–11 cases per 1000 population, with around 50,000 hospital admissions in the UK per year (1). Parapneumonic effusions caused by an infection of the pleural membranes occur in 40–57% of cases of pneumonia. A variable percentage (10–20%) of parapneumonic effusions progresses to empyema (pus) and/or abscess formation (encapsulation). Pleural infection is associated with significant morbidity and mortality which may be as high as 20–35% in immunocompromised patients (1)

Standard treatment of these collections in adults involves antibiotic therapy, effective drainage of infected fluid and surgical intervention if conservative management fails. For parapneumonic effusions which require clearance, appropriate therapy is effective drainage via an intercostal catheter (ICC) with antibiotic therapy. Frequently, simple ICC drainage is not effective due to the presence of loculations, formed predominantly by fibrinous material deposited in the fibrinopurulent phase of empyema, which prevent free drainage of infected pleural fluid (2). The presence of fibrinous septae in the pleural space, known as loculations, may result in inadequate drainage of effusions and therefore non-resolution of infection and systemic sepsis. Without effective intercostal catheter drainage, surgical intervention (VATS or open) has usually been required to clear loculations for resolution of infection.

Non-surgical treatment options to reduce the impact of adhesions and locule include (in addition to appropriate antibiotic therapy) single and multiple thoracocentesis, or single and multiple intercostal tube thoracostomies, with or without intrapleural fibrinolytic agents. Surgical options include direct-vision and VATS adhesiolysis, limited and full thoracotomy with adhesiolysis, and decortication for severe pleural thickening (3).

Although the success rate of surgical intervention remains high, the morbidity and mortality of both VATS and open thoracotomy are of concern, particularly in a cohort of patients who may be

older and with significant co-morbidity. Less invasive therapies which promote pleural space drainage and effective resolution of pleural infection are therefore likely to be of considerable clinical utility (4).

Intra-pleural fibrinolytic therapy (IPFT) in the management of complex parapneumonic effusions and thoracic empyema has been employed for over 50 years, with a mixture of agents including streptokinase/streptodornase (5), streptokinase (6,7,8,9), urokinase (10), alteplase (11,12), and a combination of streptodornase and alteplase (13). These medications are administered into the pleural space via an ICC.

Fibrinolytic agents including streptokinase, urokinase, alteplase and recombinant tissue plasminogen activator (rTPA) have been used safely and effectively intrapleurally for complicated pleural effusion and empyema (14,15,16,17). During the fibrinopurulent-purulent stage of empyema, there is an imbalance between fibrin activators and fibrin inhibitors (18), with elevated levels of plasminogen activator inhibitor (PAI-1) resulting from the presence of inflammation-induced tumour necrosis factor-alpha, interleukin 8 and transforming growth factor beta, as well as lower levels of endogenous tissue plasminogen activator (tPA) (19). This results in a pro-fibrotic state causing deposition of fibrin-forming loculations within the infected pleural space (20). Fibrinolytic agents activate plasmin, lysing fibrinous septations, thereby improving pleural fluid drainage and clearing infection without requiring surgical intervention.

MIST 2 trial has established intrapleural therapy as the mainstay of CPEE treatment hence avoiding surgery and decreasing the length of hospitalization [10,21, 22, 23, 24]; however, little is known about the correct dosage needed for tPA and DNase [25]. Dose and duration of intrapleural therapy based on MIST 2 involve multiple dosing and can be time-consuming for health care providers [21, 25]. Previous studies showed that complexity of treatment is a factor associated with poor adherence to a regimen [26]. For this reason, trying to find the minimum effective dose and simplifying the regimen is essential for minimizing side effects and maximizing adherence. The review of currently available literature shows concurrent administration of tPA and DNase to be safe and effective even at lower cumulative dose

Other study was carried out in May 2022 in which Modified regimen intrapleural alteplase 16 mg t-PA with 5 mg DNase for total 3 doses that administered sequentially within 24 h had been used. In this study, modified regimen of t-PA and DNase offer an alternative therapeutic option for patients that are unfit or refuse surgical intervention but persistent pleural infection. They have demonstrated similar treatment success comparable to other studies [24, 27, 28], as evidenced by improvement on pleural fluid drainage and reduction in pleural opacity on day 7 chest x-ray was approximately 50% from the baseline using intrapleural 16 mg t-PA with 5 mg DNase. The mechanism of action of t-PA and DNase in pleural cavity remain unclear. Studies suggested that IPFT may trigger the monocyte chemoattractant protein 1 (MCP-1) pathway which promote pleural fluid formation and subsequently causes a therapeutic lavage effect that increases pleural fluid drainage [29]

Another option for intrapleural therapy may be pleural irrigation with normal saline. The idea behind is to dilute and remove bacteria, cytokines, inflammatory cells, and pro-fibrinogenic coagulation factors, which induce pleural fluid organization. Also, the mechanical process of irrigation increases pleural fluid drainage by reducing stasis and organization of the intrapleural contents .

A randomised controlled pilot study in which saline pleural irrigation (three times per day for 3 days) plus best-practice management was compared with best-practice management alone was performed in patients with pleural infection requiring chest-tube drainage. The primary outcome was percentage change in computed tomography pleural fluid volume from day 0 to day 3. Patients receiving saline irrigation had a significantly greater reduction in pleural collection volume on

computed tomography compared to those receiving standard care. Significantly fewer patients in the irrigation group were referred for surgery (30).

However, till date there is no study done on head to head comparison between intrapleural fibrinolytic with alteplase and DNAse Versus Pleural irrigationwith normal saline.

The respiratory unit in HUKM has been using intrapleural fibrinolysis therapy with varying doses since 2017. This study aims to develop an algorithm for intrapleural therapy on pleural infection with a minimally invasive method without surgical intervention. It also aims to determine the efficacy and safety of this dose regimen of combined intrapleural Alteplase and DNase versus pleural irrigation on management of pleural infection.

# CHAPTER 2 : RESEARCH OBJECTIVES & HYPOTHESIS

## 2.1 Research Questions:

- Is the combination of intrapleural Alteplase (t-PA) 5mg and DNase (Pulmozyme) 5mg superior than pleural pleural irrigation in the management of pleural infection?

## 2.2 Primary Objective:

- To measure the volume of pleural effusion drainage (in mls) 48 hours following randomization

## 2.3 Secondary Objectives:

- To determine the reduction of pleural opacity (in percentage) on chest radiograph from day 1 (randomization) to day 7
- To determine the change on inflammatory markers (WBC/CRP) from day 1 (randomization) to day 7
- To determine the outcome :
  - Length of hospital stay (in days) after randomization for each group
  - The need of surgical intervention in 30 days
  - Adverse effects following t-PA/DNase and pleural irrigation
  - Mortality rate at 30 days

## 2.4 Study Hypothesis

1. Subjects in the IPFT has more volume of pleural fluid drainage compared with pleural irrigation group

2. Subjects in the IPFT has greater reduction of inflammatory parameters compared with pleural irrigation group

3. Subjects in the IPFT has shorter length of hospital stay compared with pleural irrigation group

4. Subjects in the IPFT has less surgical referral rate compared pleural irrigation group

5.There is no difference of mortality rate between both groups

# CHAPTER 3: METHODOLOGY

## Description of Methodology

## 3.1 Study Design

Prospective open-label study on patients with pleural infection who were given either pleural irrigation or intrapleural t-PA and DNase from **June 2023 – June 2025** in Universiti Kebangsaan Malaysia (UKM) Medical Center

## 3.2 Study Population

Adult patients with pleural infection (complex pleural effusion or empyema) with poor outflow (≤ 150 cc) from chest drain after 24 Hours of insertion in medical and non-medical wards UKMMC

## 3.3 Sample size and Power of Study

By using power and sample size programme calculator :

Prior data indicate that the failure rate among controls is 0.15. If the true failure rate for experimental subjects is 0.32, we will need to study 39 experimental subjects and 39 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with

probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.5. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis.

N = 39+/-4 (IPFT with alteplase and DNase) and 39+/-4 (pleural irrigation with normal saline)

Study used as a reference :

Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection Clare E. Hooper1,2, Anthony J. Edey3 , Anthony Wallis3 , Amelia O. Clive1,2, Anna Morley2 , Paul White4 , Andrew R.L. Medford2 , John E. Harvey2 , Mike Darby3 , Natalie Zahan-Evans2 and Nick A. Maskell1,

Reference for sample size taken from the primary outcome of this research in which patients receiving saline irrigation had a significantly greater reduction in pleural collection volume on computed tomography compared to those receiving standard care (median (interquartile range) 32.3% (19.6–43.7%) reduction versus 15.3% (−5.5–28%) reduction) ( $p<0.04$).

## 3.4 Inclusion and Exclusion Criteria

### Inclusion Criteria

1. Adult patient with aged ≥ 18 years old
2. Patients with pleural infection (complex parapneumonic effusion or empyema) with poor pleural fluid drainage of ≤ 150 ml after 24H of insertion of chest drain
3. Clinical features consistent with pleural infection ; fulfilling ≥ 2 of the following characteristics :
   - i) Clinical evidence of infection such as fever and or elevated C-reactive protein (CRP) or total white blood count (TWBC)
   - ii) Complex pleural effusion proven by thoracic ultrasound is defined as presence of fibrin strands or septations within pleural cavity
   - iii) Pleural fluid that fulfil at least one of the characteristic :
     - frank pus,
     - exudative type of pleural effusion (according to light's criteria)
     - gram stain or culture positive
     - lactate dehydrogenase (LDH) > 900U/L
     - Acidic with ph < 7.2
     - glucose level < 3.3 mmol/L

### Exclusion criteria

1. Refusal to participate
2. Known allergy to t-PA or DNase
3. Acute stroke
4. Significant bleeding diathesis/ active gastrointestinal bleed
5. Major surgery in the previous 5 days
6. Previous pneumonectomy on the infected side
7. Bronchopleural fistula
8. Pregnancy

9. Coagulapathy (INR > 2, APTT > 100)
10. Platelet count < 50000 cells

## 3.5 Problem Statement

Retained complicated pleural effusion is associated with a risk of empyema and sepsis.IPFT is commonly used as the bridging therapy to surgery. The efficacy of saline irrigation is not known. However, the probable problem in this study is when failed saline irrigation, the patient will be given IPFT as part of the intention to treat.

## 3.6 Recruitment/Data Collection

Subjects with pleural infection (complex parapneumonic effusion or empyema) with poor outflow ≤150cc pleural fluid from chest drain over 24 hours of insertion with standard medical therapy who are eligible for this study will be offered to participate into this study. Patient will be informed that this is an 'off label' drugs and a written informed consent will be obtained.

All patients will undergo chest tube/drain insertion. The decision to insert chest drain, the size of chest drain and when to initiate intrapleural t-PA/DNase is determined by the chest physician.

Ultrasound of thorax and chest radiograph will be performed within 24hours before randomization. Ultrasound of thorax is performed by chest physician with curve probe (ultrasound Mindray, model Z5) for confirmation of complex pleural effusions and chest tube's position. Complex pleural effusion on ultrasound is defined as fibrin strands or septa within the pleural effusion along with presence of loculations in pleural cavity. A baseline chest radiograph will be performed within 24 hours prior to intrapleural fibrinolysis or pleural irrigation to ensure the chest tube position.

Demographic data was collected prior to randomization, which consist of age,gender,ethnicity,BMI,comorbidities. Subjects will be randomized with a block of 4 (using sealed envelope) with random permutations of 2 groups : pleural irrigation group and intrapleural t-PA and DNase.

All patients that prescribed intrapleural t-PA/DNase during the study period will receive a standard dose of medications as below (Appendix 1).

Medication Regimen :

t-PA (Alteplase) 5mg and DNase (Pulmozyme)5mg

t-PA (Alteplase) that is available in our pharmacy is 50mg ampoule and DNase (Pulmozyme) is 2.5mg per ampoule

The number of installation of intrapleural t-PA/DNase depends on the discretion of the treating physician (at least 6 hours apart between each dose). 5mg of Alteplase (t-PA) and 5mg DNase are diluted in each 50ml of 0.9% sodium chloride solution. t-PA and DNase are not mixed together in one syringe. The detailed method of t-PA/DNase therapy administration is described in Appendix 1. In brief , both medication are administered sequentially which t-PA is first instilled intrapleurally and the chest tube is then clamped for 45 minutes, then unclamped to allow free drainage for 45 minutes. The same procedure is then repeated for DNase. Selection of the timing of treatment and removal of chest tube are depending on the chest physician's judgement.

However, as for patients who were randomized into pleural irrigation group, subjects were administered 250 ml of 0.9% sodium chloride via chest tube a three way tap from a drip stand which were allowed drainage freely over 1 hour. Pleural irrigation will be performed minimum of 3 installations and maximum of 9 installation (3 times per day).

Both groups received standard care of treatment : which includes regular flushing of chest drain to maintain patency using 20mls of normal saline.

The primary outcome was to evaluate the volume of pleural effusion drainage (in mls) 72 hours following randomization. The volume drained measured after subtracting the amount of volume administered as per protocol.

The secondary outcome are measured by the change in the area of pleural opacity in chest x-ray (day 7 post t-PA/DNase compared to baseline), measured as the percentage of the ipsilateral hemithorax occupied by effusion. The area of pleural opacity and the area of the ipsilateral hemithorax will be measured digitally by two radiologists using Horos Project Software, v3.2.1 as described previously in Multicentre Intrapleural Sepsis Trial 2 (MIST-2)

Other outcomes that will be monitored include :

1. Inflammatory markers including serum C-reactive protein (CRP) & white blood count
2. Length of hospital stay in days
3. The need of surgical intervention within 30 days
4. Adverse effects :
    a. Chest pain required escalation of analgesics
    b. Systemic bleeding
    c. Pleural bleeding

During any point of treatment subjects will be allowed to cross-over and analysis will be done as per intention to treat. Subjects in the pleural irrigation group may be switched to IPFT group if there is poor response to treatment (poor drainage of effusion), or adverse effects of irrigation as per clinician's judgement. On the contrary, subjects in the IPFT group may be switched to pleural irrigation group if patient developed any adverse effects of IPFT (e.g hemothorax,haemoptysis). Those who failed both treatment will be referred for surgical intervention

Monitoring Parameters :

a. Pleural irrigation group

| Parameter | Day0 | Day1 | Day2 | Day3 | Day7 | Day30 |
|---|---|---|---|---|---|---|
| **Investigations** | | | | | | |
| • Full blood count (FBC)<br>o WBC<br>o Hemoglobin | √ | √ | √ | √ | √ | |
| • C- reactive protein (CRP) | √ | | | | √ | |
| • Chest X-ray | √ | | | | √ | |
| • Ultrasound Thorax | √ | √ | √ | √ | | |
| **Adverse effects** | | | | | | |
| • Chest pain required escalation of analgesics | | √ | √ | √ | | |
| • Gastrointestinal bleed | | √ | √ | √ | | |
| • Bleeding from chest drain site | | √ | √ | √ | | |
| • Intrapleural hemorrhage | | √ | √ | √ | | |
| • Hemoptysis | | √ | √ | √ | | |
| • Clinical deterioration – hypotension, dyspnea | | √ | √ | √ | | |
| • Hb drop >10% required transfusion blood | | √ | √ | √ | | |
| • Death related to intrapleural saline irrigation | | √ | √ | √ | | |

| **Others Outcome** | | | | | | |
|---|---|---|---|---|---|---|
| • Mortality | | | | | | |
| • Surgical intervention | | | | | | |

b. IPFT group

| Net Volume of pleural fluid drained (ml) post pleural irrigation | **Baseline** | **Day 1** | **Day 2** | **Day 3** |
|---|---|---|---|---|
| | √ | √ | √ | √ |
| Cumulative pleural fluid drained post pleural irrigation | | | | √ |

b. Intrapleural fibrinolytic group

| **Parameter** | **Day0** | **Day1** | **Day2** | **Day3** | **Day7** | **Day30** |
|---|---|---|---|---|---|---|
| **Investigations** | | | | | | |
| • Full blood count (FBC)<br>o WBC<br>o Hemoglobin | √ | √ | √ | √ | √ | |
| • C- reactive protein (CRP) | √ | | | | √ | |

| | | | | | | |
|---|---|---|---|---|---|---|
| • Chest X-ray | √ | | | | √ | |
| • Ultrasound Thorax | √ | √ | √ | √ | | |
| **Adverse effects** | | | | | | |
| • Chest pain required escalation of analgesics | | √ | √ | √ | | |
| • Gastrointestinal bleed | | √ | √ | √ | | |
| • Bleeding from chest drain site | | √ | √ | √ | | |
| • Intrapleural hemorrhage | | √ | √ | √ | | |
| • Hemoptysis | | √ | √ | √ | | |
| • Clinical deterioration – hypotension, dyspnea | | √ | √ | √ | | |
| • Hb drop >10% required transfusion blood | | √ | √ | √ | | |
| • Death related to intrapleural therapy | | √ | √ | √ | | |
| **Others Outcome** | | | | | | |
| • Mortality | | | | | | |
| • Surgical intervention | | | | | | |

| | | | | |
|---|---|---|---|---|
| Net Volume of pleural fluid drained (ml) post IPFT | **Baseline** | **Day 1** | **Day 2** | **Day 3** |
| | √ | √ | √ | √ |
| Cumulative pleural fluid drained post IPFT | | | | √ |

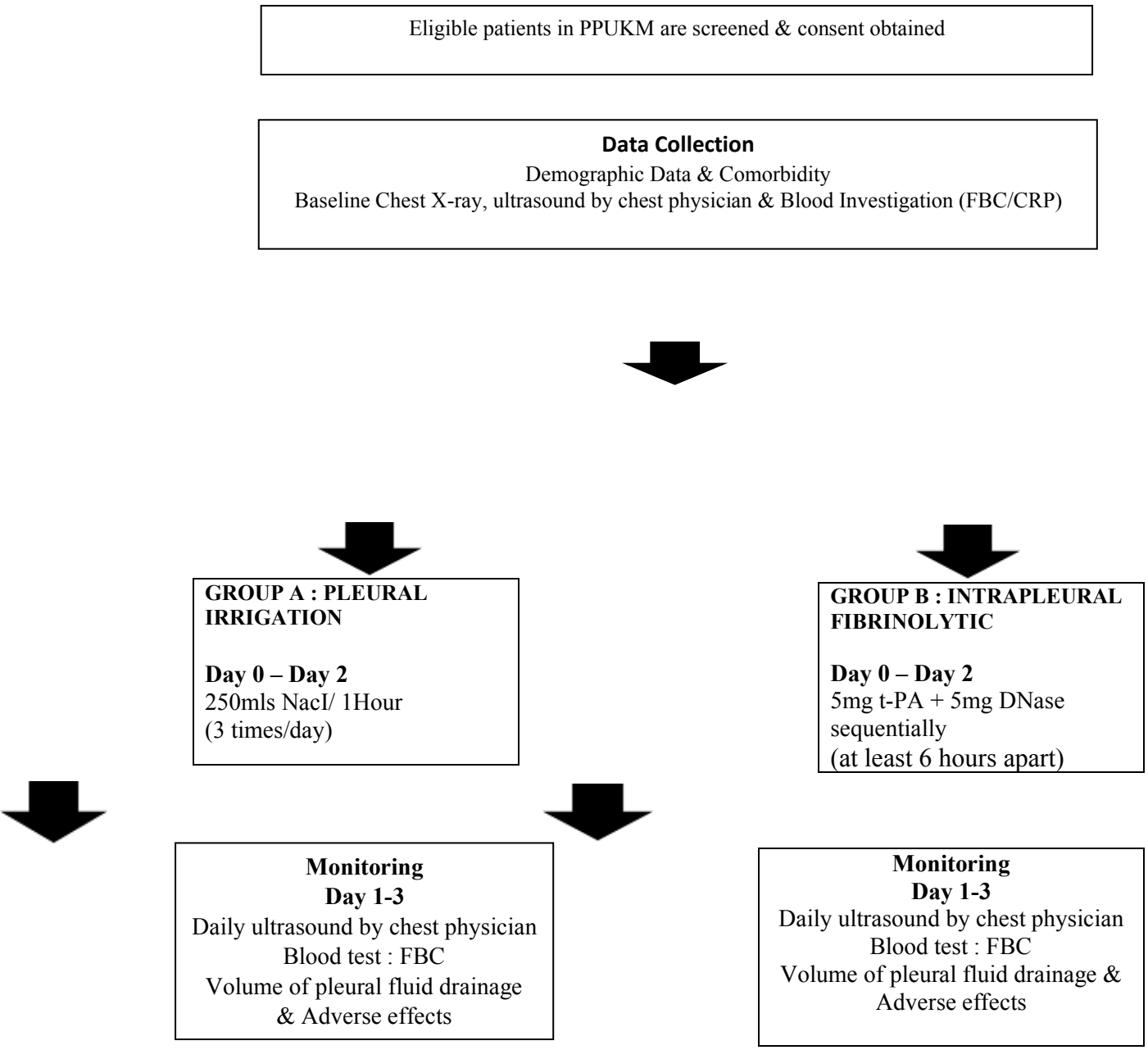
Operational Definition:

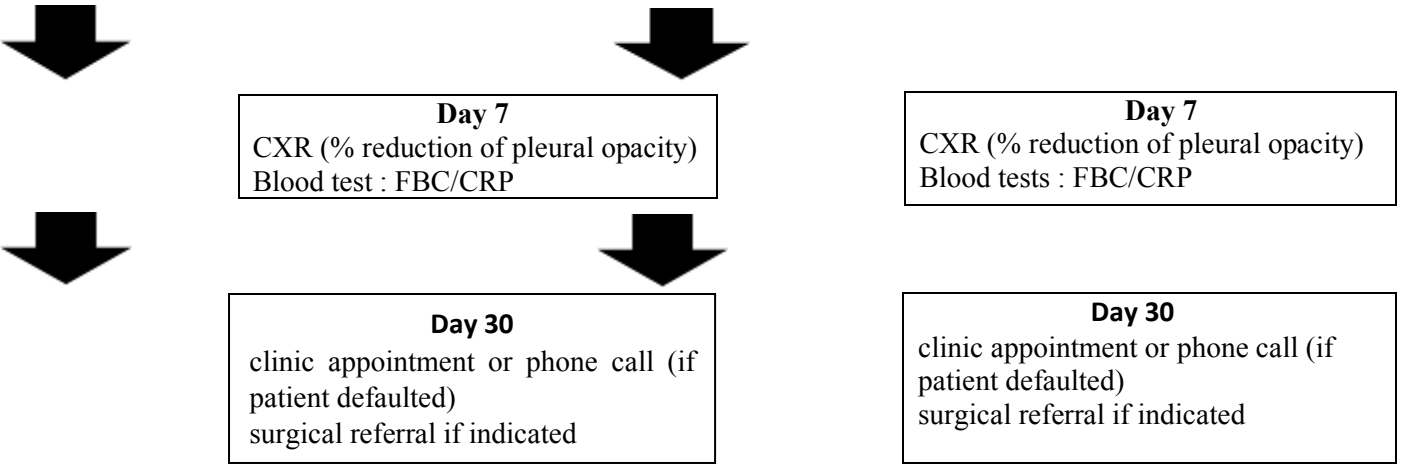
- Treatment success: significant amount of pleural drainage post intervention, reduction of opacity on chest x-ray and resolution of inflammatory markers on day 7 without surgical intervention within 30days
- Treatment failure:
    - Poor drainage from chest drain, failure of resolution of pleural effusion or empyema at least 50% reduction on opacity on chest x-ray and clinical evidence of ongoing infection that requires surgical intervention within 30days post randomization or death before discharge.

All patients will be followed up in respiratory clinic day 30 after discharge or phone call if patient defaulted clinic appointment.

Data will be collected prospectively (Appendix 5) by reviewed patient demographics, clinical data on length of hospital stay, pleural fluid analysis, intrapleural therapy, radiographic characteristics,adverse events, Laboratory data (blood leukocyte count, C-reactive protein, haemoglobin level), Intrapleural therapy data including number of chest tubes, duration of chest tube in pleural cavity and cumulative volume of pleural fluid drained. Besides that, length of hospital stay, treatment outcomes, surgical interventions and the occurrence of complications are recorded.

## 3.7 Study protocol /flow chart






## 3.7 Statistical Analysis

Statistical analysis will be performed using the available SPSS software version 19. All numerical data will be subjected to normality testing using Shapiro-Wilk test. All normally distributed data will be expressed as mean ± standard deviation (SD) whereas non-normally distributed data were expressed as median (IQR). For normally distributed data, parametric test with Student's t-test will be used. For non-normally distributed data, the Mann- Whitney test will be used or equivalent nonparametric tests. Within groups, the Wilcoxon rank sum test will be used. For qualitative data, Chi-Square test and Fisher's Exact test will be used. The significant p-value will be taken as <0.05 or in the case of multiple comparisons it will be adjusted with a Bonferonni correction.

## 3.8 Estimated cost of study

| MAIN ITEM | JUSTIFICATION | Unit | TOTAL (RM) |
|---|---|---|---|
| t-PA (Alteplase) 50mg<br>(Per vial) | Intrapleural fibrinolysis drug<br>(5 vials) | RM 2550.12 | RM 12750.60 |
| DNase 2.5mg per ampoules<br>(1 pack contains 6 ampoules of DNase) | Intrapleural fibrinolysis drug<br>(86 ampoules) | RM 190.90 | RM 8208.7 |

| | | |
|---|---|---|
| Total (RM) | | RM 20 959.30 |

## 3.9 Research ethics

The study will commence upon approval from the Ethics and Research Committee in UKMMC.

# CHAPTER 4: GANTT CHART

| **Progression / Timeline** | **Nov 2022 - Jan 2023** | **Jan - June 2023** | **June 2023** | **June 2025** | **July-Nov 2025** | **Nov 2025** |
|---|---|---|---|---|---|---|
| Formulating research title and literature review | | | | | | |
| Proposal write up and editing | | | | | | |
| Proposal presentation and modification | | | | | | |
| Proposal submission and ethic committee approval | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Commencement of study and data collection | | | | | | |
| Data analysis | | | | | | |
| Thesis write up / Dissertation preparation | | | | | | |
| Dissertation presentation and submission | | | | | | |

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30.Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline versus standard care in patients with pleural infection Clare E. Hooper1,2, Anthony J. Edey3 , Anthony Wallis3 , Amelia O. Clive1,2, Anna Morley2 , Paul White4 , Andrew R.L. Medford2 , John E. Harvey2 , Mike Darby3 , Natalie Zahan-Evans2 and Nick A. Maskell1,adults. Thorax 2001;56(Suppl. 4):IV1–64plasminogen activator and DNase in pleural infection. *N Engl J Med.* 2011;365:518–526.

# APPENDIX 1 :

**DRUG ADMINISTRATION OF INTRAPLEURAL t-PA (ALTEPLASE) & DNase (PULMOZYME)**

<table>
<tr><td>Drugs dosage</td><td>Intrapleural t-PA 5mg per dose<br>Intrapleural DNase 5mg (2 ampoules of 2.5mg) per dose<br>at least 6 hrs apart<br>Timing of administration: 8-9 am, 4-5 pm & next day 8-9am.</td></tr>
<tr><td>Patient undergoing hemodialysis</td><td>No dosage adjustment provided. Suggest for heparin free dialysis while receiving t-PA and DNase</td></tr>
<tr><td>Patient on anticoagulant</td><td>No standard guideline. Physician to assess patient‘s thrombotic risk & bleeding risk and decide if need to withhold anticoagulant.
<table>
<tr><td></td><td>Elimination half life</td></tr>
<tr><td>Warfarin</td><td>20-60 hours</td></tr>
<tr><td>Rivaroxaban</td><td>5-9 hrs ; Elderly: 11-13 hrs; renal impairment: 8.7-9.5 hrs; hepatic impairment: 10.1-10.4 hrs)</td></tr>
<tr><td>Apixaban</td><td>~12 hrs (8-15 hrs)</td></tr>
</table></td></tr>
</table>

| | | | |
|---|---|---|---|
| | | Dabigatran | 12 -17 hrs; Elderly: 14-17 hrs; Mild-to-moderate renal impairment: 15-18 hrs; Severe renal impairment: 28 hrs |

**MATERIAL REQUIREMENT:**

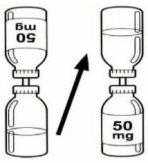
1. Drugs as prescribed
2. Dressing pack
3. Sterile gloves
4. Povidone iodine 10% or Chlorhexidine in 70% alcohol or alcohol swab
5. 2 x 50ml leur lock syringes (for Alteplase & Pulmozyme)
6. 2 x 10ml syringes (to flush)
7. 2 x Blunt ended drawing up needles
8. 0.9% NaCL total 750ml
9. 3-way tap connector
10. Rubbish bag
11. Dressing trolley

## 1. PREPARATION CHART t-PA (ALTEPLASE)/ACTILYSE®:

### A) Reconstitution

1) Wipe the top of the vial with 60-70% alcohol swab.
2) Insert cannula into **Sterile Water Vial** (provided in the box).

3) Empty water into **Actilyse® 50mg Vial**.

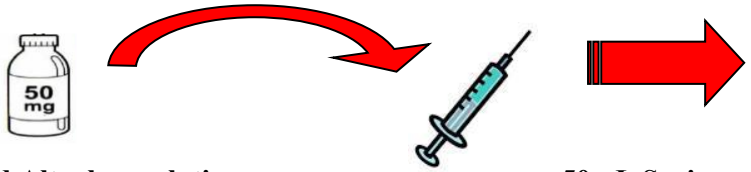



4) Mix by gentle swirling/ slow inversion. **DO NOT** shake. Allow to stand if foam is present. Final concentration = **1mg/mL (50mL)**.


### B) Administration

**STEP 1**

Syringe out **dose** required (eg: if 16 mg = 16 ml)




**Reconstituted Alteplase solution** 1mg/mL (50mL)

**50mL Syringe**


Further dilute with normal saline up to **final volume of 50ml**

**STEP 2**

Wrap balance Alteplase solution with parafilm, label date and time open and keep in fridge. (stable for 24 hours)

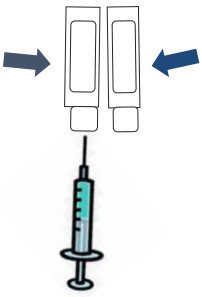
## 2. PREPARATION CHART – DNase (PULMOZYME) :

- DNase (Pulmozyme) must be stored **in the refrigerator** at **2-8°C** and protected from light & heat.
- Do not use the medicine if it has been exposed to room temperature for more than 24 hours.
- The solution should be discarded if it is cloudy or discoloured.
- DNase (Pulmozyme) contains no preservative and, once opened, the entire ampoule must be used or discarded.

a) Open the foil pouch and remove only **2 ampoules (2x2.5mg=5mg)** of DNase (Pulmozyme) from its pouch each time before instillation. Keep the other ampoules back into fridge.

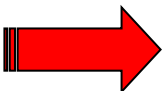

b) Hold the tab at the base of the ampoule of DNase (Pulmozyme) firmly, taking care not to squeeze the body of the ampoule, and twist off th


c) Syringe out the full dose of the drug from 2 ampoules of DNase (Pulmozyme) (2 x 2.5ml) until the ampoule is empty.



Turn the ampoule upside down and gently squeeze.

**Syringe out all the contents from 2 ampoules (2x 2.5ml=5ml =5mg) into syringe.**



**50mL Syringe**


Further dilute with normal saline to **final volume of 50ml**

**d)** Wrap the 50ml syringe with diluted DNase (Pulmozyme) with parafilm, label date and time of preparation. Do not use the medicine if it has been exposed to room temperature for more than 24 hours.

## PROCEDURE OF INSTILLATION OF t-PA/DNase

1. Premedication (Tramadol) for pain relieve before each dose. Medication to be given at least 20 minutes before the procedure.
2. Draw up Alteplase & DNase as prescribed (Refer Section 6 & 7 of protocol).
   Prepare 2 x 10ml 0.9% NaCL in syringes for flushing purpose.
3. Check all connections are secure.
4. Uncap the outer port.
5. Clean the port thoroughly with Chlorhexidine, Povidone iodine 10% or alcohol swab.
6. Turn the 3-way tap to off the position to the chest.
7. Attach the 10cc syringe filled with NS to the outer port and turn the 3 way tap towards the chest.
8. Flush the drain with 5 ml NaCL (pre-Alteplase) to check patency.
9. Turn the 3 way tap to off the position to the chest.
10. Attach 50cc syringe containing diluted Alteplase, turn back the 3 way tap towards the chest and inject slowly within 1-2 minutes.
11. Disconnect and flush with 5ml NaCL towards the chest (post-Alteplase).
12. After flushing, keep the 3-way tap turned off to the chest and clamp for 45 minutes.
13. Attach new bung to the outer port.
14. After clamping, open the 3-way tap to drain towards the bottle for 45 minutes, record drainage prior to second instillation.
15. After 45 minutes of drainage, repeat process with DNase (Pulmozyme). Flush the drain with 5 ml NS (pre-Pulmozyme).
16. Turn the 3 way tap to off the position to the chest.
17. Attach 50cc syringe containing diluted DNase (Pulmozyme), turn back the 3-way tap towards the chest and inject slowly within 1-2 minutes. Followed by a 5ml NS flush (post-Pulmozyme).
18. After flushing, keep the 3-way tap turned off to the chest.
19. After 45 minutes of clamping, open the 3-way tap to drain towards the bottle and record the drainage until next instillation.

## OBSERVATION AFTER ADMINISTRATION OF t-PA (ALTEPLASE) & DNase (PULMOZYME)

1. Observe the patient for:
   a. deterioration in clinical condition
   b. tension pneumothorax
   c. hemorrhage from site or excessive drainage (in excess of 1L per hour) in drainage bottle

2. Monitor for:
   a. Bedside ultrasound of thorax (by chest physician) daily with curvelinear probe (ultrasound Mindray, model Z5) by measuring the maximum distances between the parietal and visceral pleural.
   b. Serial chest x-ray (baseline x-ray, day 7 post t-PA/DNase and pleural irrigation)
   c. Serum CRP level (baseline, day 7 post t-PA/DNase and pleural irrigation)
   d. FBC (baseline, day 1- 3, day 7 post t-PA/DNase and pleural irrigation). Drop of

hemoglobin by less than 10% from baseline is acceptable.

e. Systemic bleeding/ Pleural bleeding
f. Drainage of pleural effusion daily

3. Stop the t-PA & DNase if there is significant drop of haemoglobin (>10% drop Hb) with clinical signs of shock or significant haemorrhagic fluids drained. Consider CTA and blood transfusion in those cases

## Data Collection Sheet

**Open label controlled trial of pleural irrigation with normal saline versus intrapleural fibrinolytic with tissue plasminogen activator and DNase in Pleural Infection in Universiti Kebangsaan Malaysia Medical Centre (UKMMC)**

Patient's ID sticker

| | |
|---|---|
| Date of admission: | Admission ward: |
| Date of discharge : | Phone number: |

Inclusion criteria

- ☐ Adult patient with aged ≥ 18 year old
- ☐ History of fever and /or elevated inflammatory markers such as elevated CRP/WBC
- ☐ Radiological evidence of complicated pleural effusion or empyema

Exclusion criteria

- ☐ Known allergy or sensitivity to DNase or t-PA
- ☐ Acute stroke
- ☐ Major haemorrhage or major trauma in last 6 months

| |
|---|
| Information sheet given ☐ If yes, proceed to data collection ⇨ |

| **Demographic** | |
|---|---|
| Gender | Male / Female |
| Age | Years |
| Ethnicity / Race | Malay ☐<br>Chinese ☐<br>India ☐<br>Others ☐ |
| Occupation | |
| Smoking history | Smoker ☐ …… packs/year<br>Ex- smoker ☐ …….packs/year<br>Non smoker ☐ |
| Allergy history<br>(If yes, state the name of drugs/food) | |

| ✓ **Tick the appropriate box** | **Yes** | **No** |
|---|---|---|

| **Comorbidities** | | |
|---|---|---|
| Diabetes mellitus | | |
| Hypertension | | |
| Dyslipidemia | | |
| Ischemic heart disease | | |
| Congestive cardiac failure (CCF) | | |
| Stroke/ TIA > 3 months duration | | |
| Atrial fibrillation<br>(If yes, state type of anticoagulant) | | |
| Valvular heart disease | | |
| Bronchial asthma | | |
| Chronic obstructive lung disease (COPD) | | |
| Lung fibrosis | | |
| History of pulmonary tuberculosis<br>(If yes, state whether on treatment) | | |
| Chronic liver disease | | |
| End stage renal disease | | |
| Malignancy<br>If yes, state site of primary disease & stage, whether chemo/radiotherapy? | | |

| **Medications/ drug history:** | |
|---|---|

## Outcome Monitoring:

| Parameter | Day0 | Day1 | Day2 | Day3 | Day7 | Day30 |
|---|---|---|---|---|---|---|
| **Investigations** | | | | | | |
| • Full blood count (FBC)<br>o WBC<br>o Hemoglobin | | | | | | |
| • C- reactive protein (CRP) | | | | | | |
| • Chest X-ray | | | | | | |
| • Ultrasound Thorax | | | | | | |
| **Adverse effects** | | | | | | |
| • Chest pain required escalation of analgesics | | | | | | |
| • Gastrointestinal bleed | | | | | | |
| • Bleeding from chest drain site | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| • Intrapleural hemorrhage | [redacted] | | | | [redacted] | |
| • Hemoptysis | | | | | | |
| • Clinical deterioration – hypotension, dyspnea | | | | | | |
| • Hb drop >10% required transfusion blood | | | | | | |
| • Death related to intrapleural therapy | | | | | | |
| **Others Outcome** | | | | | | |
| • Mortality | [redacted] | | | | | |
| • Surgical intervention | | | | | | |

| Net Volume of pleural fluid drained (ml) post pleural irrigation | **Baseline** | **Day 1** | **Day 2** | **Day 3** |
|---|---|---|---|---|
| | | | | |
| Cumulative pleural fluid drained post pleural irrigation | [redacted] | | | |

| **Other Outcome Measures** | |
|---|---|
| Duration of hospital stay from 1st dose of intrapleural t-PA/Dnase or 1st pleural irrigation | Days |
| Requirement of surgical intervention within 30days from 1st dose t-PA/DNase or 1st pleural irrigation (normal saline 0.9%) | Yes / No<br><br>If yes,<br>Decortication ☐<br>Pneumonectomy ☐<br>Lobectomy ☐ |
| Outcome upon discharge | Alive ☐<br>Death ☐ |
| Readmission within 30 days from discharge for similar complaint (recurrent parapneumonic effusion/empyema) | Yes / No |

| | |
|---|---|
| Complete resolution on radiologically (chest x-ray) on clinic appointment | Yes / No |
| Mortality within 30 days (from 1st dose intraplural t-PA/Dnase or normal saline 0.9%) & cause | |

| | | |
|---|---|---|
| **Treatment outcome** | Successful | ☐ |
| | Failure | ☐ |